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Efficacy evaluation of prophylactic cranial irradiation for limited stage small-cell lung cancer in the magnetic resonance imaging era: A meta-analysis

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Abstract. The role of prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer (LS-SCLC) remains controversial in the era of magnetic resonance imaging (MRI). The present study aimed to evaluate the effectiveness of PCI in the treatment of LS-SCLC in the era of MRI. The PubMed, EMBASE and Cochrane Library databases were searched from the time of database creation until May 24, 2023, to identify clinical studies that evaluated the effectiveness of PCI in patients with LS-SCLC in the MRI era. The references of the obtained studies were also reviewed to identify clinical studies that were not discovered in the initial search. All studies were screened in accordance with the inclusion criteria, and the data were extracted and subjected to meta-analysis using STATA17.0. In total, 21 studies were included in the analysis. Notably, 10 studies only used brain MRI at baseline to confirm the absence of brain metastases (BMs; pre-chemoradiotherapy MRI group), 7 studies used brain MRI prior to PCI to confirm the absence of BMs (pre-PCI MRI group) and 4 studies used active surveillance in the form of brain MRI following PCI (MRI surveillance group). The results of the meta-analysis demonstrated that for all included patients, PCI was associated with a significant improvement in overall survival time [OS; hazard ratio (HR), 0.61; confidence interval (CI), 0.53-0.70] and progression-free survival (HR, 0.69; CI, 0.61-0.79), as well as a significant decrease in the rate of BM (HR, 0.59; CI, 0.50-0.70). Subgroup analyses revealed that PCI remained effective in improving OS and reducing the rate of BM in patients with LS-SCLC who did not have BMs confirmed via brain MRI performed at baseline or prior to PCI. However, in the MRI surveillance group, PCI failed to significantly improve the OS (HR, 0.65; CI, 0.41-1.05), despite significantly reducing the BM rate (HR, 0.6; CI, 0.45-0.8) of LS-SCLC. Collectively, the results of the present study demonstrated that PCI remained effective in improving OS and reducing the rate of BM in patients with LS-SCLC who had the absence of BM confirmed via brain MRI at baseline or prior to PCI. Additionally, in patients with LS-SCLC who had undergone active surveillance using brain MRI following PCI, the incidence of BM was reduced, while the OS was not significantly improved. However, additional randomized controlled clinical studies are required to verify these findings.

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Introduction

Small-cell lung cancer (SCLC) accounts for 13-15% of all lung cancer cases and approximately one-third of cases are limited-stage (LS)-SCLC (1). LS-SCLC has a poor prognosis due to rapid growth and early distant and loco-regional dissemination. The median survival time of LS-SCLC is reported to be 16-20 months with a 5-year survival rate of 10-20% (2). Brain metastasis (BM) is a common complication of SCLC, occurring either at diagnosis or throughout the course of the disease (3). Additionally, >10% of patients with SCLC have BM at initial diagnosis and the cumulative incidence of BM at 2 years is >50% (4). Furthermore, ~65% of patients have detectable BM on autopsy (5). The survival advantage of prophylactic cranial irradiation (PCI) was first demonstrated in the 1990s and a 5.4% increase in the rate of survival was acquired at 3 years among patients with SCLC in complete remission (6). The National Comprehensive Cancer Network guidelines recommend PCI as the standard treatment for patients with LS-SCLC who have achieved remission after first-line chemoradiation therapy (7). However, these guidelines are primarily based on the results of a meta-analysis of multiple clinical studies conducted in the pre-magnetic resonance imaging (MRI) era (6,8). During this phase, the enrollment criteria were based on the absence of symptoms of BM or the use of computed tomography (CT) imaging to confirm the absence of BM, rather than MRI examination. In addition, the results of a previous study revealed that the detection rate of BM was 10% in the CT era and 24% in the MRI era (9), indicating that MRI may be more sensitive than contrast-enhanced CT for the detection of BMs. Thus, MRI may be more beneficial as an assessment tool for BM. Numerous previous retrospective studies conducted in the MRI era have re-evaluated the efficacy of PCI in patients with LS-SCLC (10-30). Some of these studies (10,15,18,20,26) suggest that PCI fails to significantly prolong the overall survival (OS) time of patients with LS-SCLC in modern pretreatment MRI staging. However, other studies (21-25,27-30) suggest that PCI does significantly prolong the OS time of patients with LS-SCLC in the era of MRI. As such, the results of these studies remain controversial. Therefore, the present study aimed to evaluate the efficacy of PCI in patients with LS-SCLC in the era of MRI, to provide a reference for the clinical management of LS-SCLC.

Materials and methods

Literature search strategy. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.cochranelibrary.com/) and Cochrane Library (https://www.embase.com/) databases were searched for clinical studies assessing the effectiveness of PCI in patients with LS-SCLC during the MRI era, from the time of database creation until May 24, 2023. The references of the obtained studies were also examined for the identification of pertinent clinical studies that were not discovered during the initial search. Search terms included 'small-cell lung carcinoma', 'small-cell lung cancer', 'prophylactic brain irradiation', 'prophylactic cranial irradiation', 'PCI' and 'whole-brain radiotherapy'. A combination of subject terms and key words were used in the search.

Inclusion and exclusion criteria. Literature were included in the present study according to the following criteria: i) Studies involving patients with LS-SCLC; ii) studies involving patients without BM, as confirmed using brain MRI at baseline or prior to PCI; iii) clinical trials evaluating the effectiveness of PCI in the treatment of LS-SCLC compared with non-PCI; and iv) clinical trials reporting outcomes, such as overall survival (OS) and the rate of BM. The following literature were excluded from the present meta-analysis: i) Abstracts; ii) case reports; iii) reviews; iv) study plans; v) studies that reported outcomes yet withheld raw data; and vi) studies that were not available in English.

Literature screening and data extraction. In total, two researchers independently evaluated the literature and extracted data from the included studies. When a consensus on inclusion could not be reached, discussions were held within the research group. Primary information that were extracted from the literature was as follows: i) General information, including author names, year of publication, type of study, number of patients, patient sex, patient age and patient history of smoking; ii) clinical information, including tumor stage, initial treatment, percentage of complete response (CR) and partial response (PR) and PCI dose; and iii) outcome indices, including OS, progression-free survival (PFS), BM rate and BM-free survival (BMFS). The Newcastle-Ottawa scale (NOS) was used to assess the quality of each study (31), and those scored with seven stars or more were considered to be high-quality studies.

Statistical analysis. Statistical analysis was performed using STATA 17.0 software (StataCorp LP). The included studies that provided OS-related hazard ratios (HRs) and 95% confidence intervals (CIs) were analyzed during the meta-analysis. For studies that only provided Kaplan-Meier survival curves, the associated HR and 95% CI were calculated using Engauge Digitizer v12.2.1 software (http://markummitchell.github.io/engauge-digitizer/) and methods as previously described (32). χ^2 test and the I^2 index were used to investigate heterogeneity. The Cochrane Guidance Manual for Systematic Evaluation (33) states that the significance level of heterogeneity should be set at P=0.1 for the χ^2 test and I^2 should be set at 50%. However, according to the recommendations provided by the Cochrane Handbook for Systematic Reviews of Interventions (33), the choice between a fixed-effect and a random-effects meta-analysis model should not be made on the basis of a statistical test for heterogeneity. Additionally, heterogeneity is always expected when examining the intervention effects among multiple studies from different research groups and geographical locations. Therefore, all data for the present meta-analysis were combined using the random-effects model. Publication bias was evaluated using a funnel plot.

Results

Literature screening and baseline characteristics. A total of 21 retrospective clinical studies assessing the therapeutic efficacy of PCI in patients with LS-SCLC during the MRI era were included in the present study. The screening process is outlined in Fig. 1 and the baseline characteristics of the included studies are displayed in Table I. All patients with LS-SCLC included in the 21 retrospective studies underwent baseline or pre-PCI brain MRI to exclude the presence of BM. In total, 10 of the studies only used brain MRI at baseline to confirm the absence of BM, 7 studies used brain MRI prior to PCI and at baseline to confirm the absence of BM and only 4 studies used brain MRI as active surveillance following PCI. In 1 study, the initial treatment regimen consisted of surgery plus chemotherapy, 2 studies used surgery plus chemotherapy and the remaining 18 studies used chemoradiotherapy. In 10 of the included studies, the PCI dose was 25 Gy/10 fractions (F), compared with 30 Gy/15 F in 2 studies, and between 25 and 40 Gy in 5 studies. Notably, the PCI dose was not reported in the remaining 4 studies. The quality of all included trials was evaluated using the NOS (8) and all were rated as high quality. The results of the quality assessment are displayed in Table SI.

Overall outcomes. The results of the present study revealed that the 1-, 2-, 3- and 5-year OS rates of patients in the PCI groups were 89, 67, 50 and 40%, respectively (Fig. S1), while in the non-PCI group the OS rates were 85, 48, 35 and 32% (Fig. S2). In addition, the combined HR was 0.61 (CI, 0.53-0.70; P<0.001; Fig. 2). Only 8 of the included studies performed propensity-matched analysis, and the combined

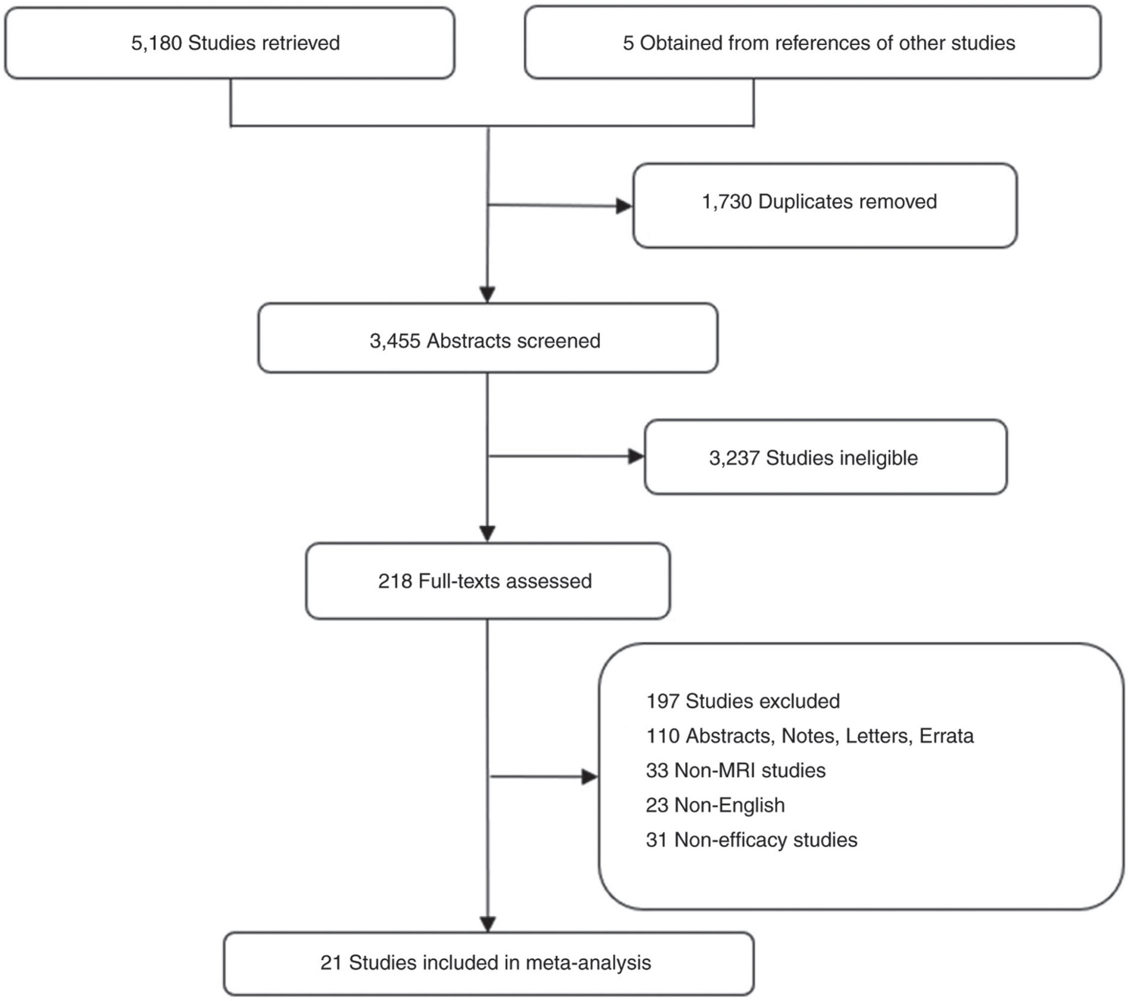

Figure 1. Flow chart of the literature screening.

results demonstrated that PCI significantly improved the OS of patients with LS-SCLC (HR, 0.73; CI, 0.62-0.88; P=0.001; Fig. 3). The 1-, 2-, 3- and 5-year BM rates in the PCI groups were 6, 18, 20 and 25%, respectively (Fig. S1), while in the non-PCI group the BM rates were 29, 38, 27 and 41% (Fig. S2). Notably, PCI significantly reduced the incidence of BM in patients with LS-SCLC (HR, 0.55; CI, 0.46-0.67; P<0.001; Fig. 2). The combined results also demonstrated that the PFS (HR, 0.69; CI, 0.61-0.79; P<0.001) and BMFS (HR, 0.39; CI, 0.24-0.62; P<0.001) in the PCI group were significantly improved compared with the non-PCI group (Fig. 2).

Results of the pre-chemoradiotherapy (CRT) MRI group. In total, 10 studies included patients who had undergone brain MRI at baseline, which excluded the presence of BM. The combined results of these studies revealed that the 1-, 2-, 3- and 5-year OS rates of patients in the PCI groups were 84, 61, 50 and 36%, respectively (Fig. S3), while in the non-PCI group the OS rates were 82, 42, 33 and 27% (Fig. S4). In addition, the combined HR was 0.58 (CI, 0.50-0.68; P<0.001; Fig. 4). Notably, the propensity-matched analysis of 1 study revealed a significant increase in OS in patients in the PCI group (HR, 0.64; CI, 0.43-0.95; P=0.027; Fig. 3). The combined results revealed that the PCI group exhibited a significantly lower BM rate than the non-PCI group, with 1-, 2-, 3- and 5-year BM rates of 8, 14, 23 and 24%, respectively (Fig. S3), while in the non-PCI group the BM rates were 23, 27, 27 and 40% (Fig. S4). In addition, the combined HR was 0.54 (CI, 0.41-0.72; P<0.001; Fig. 4). Moreover, the PFS (HR, 0.61; CI, 0.48-0.79; P<0.001) and BMFS (HR, 0.39; CI, 0.18-0.84; P=0.016) rates observed in the PCI group were significantly improved, compared with the non-PCI group (Fig. 4).

Results of the pre-PCI MRI group. The pooled analysis included 7 trials that comprised of patients without BM, verified using brain MRI prior to PCI. The results revealed that the 1-, 2-, 3- and 5-year OS rates of patients in the PCI groups were 89, 78, 57 and 54%, respectively (Fig. S5), while in the non-PCI group the OS rates were 83, 58, 60 and 42% (Fig. S6). In addition, the combined HR was 0.63 (CI, 0.49-0.81; P<0.001; Fig. 5). Propensity-matched analysis was carried out in 4 of the 7 studies that used brain MRI prior to PCI to confirm the absence of BMs, and the combined results also revealed that the OS was significantly higher in the PCI group (HR, 0.77; CI, 0.60-0.99; P=0.039; Fig. 3). The 1-, 2-, 3- and 5-year BM rates of patients in the PCI groups were 4, 26, 16 and 18%, respectively (Fig. S5), while in the non-PCI group the BM rates were 31, 40, 21 and 39% (Fig. S6). The combined HR was 0.43 (CI,

Table I. Baseline characteristics of the included studies.

First author, year	Group	Time frame of the study	Patients, n	Median age (range), years	Male/ female	I-II/III	CCRT/ SCRT	EP/ others	CR/PR	PCI dose, Gy/F	Brain MRI time points	(Refs.)
Chen *et al*, 2022	PCI	2009.6-2019.6	324	58.0 (51-64)	232/92	62/162	115/209	315/9	91/233	25-30/10	Baseline, before PCI,	(10)
	Non-PCI		324	59.0 (51-65)	229/95	54/270	132/192	305/15	99/225		MRI surveillance	
Eze *et al*, 2017	PCI	1998-2012	71	-	36/35	-	34/37	68/3	-	30/15	Baseline, before PCI	(11)
	Non-PCI		113	-	75/38	-	35/78	96/17	-			
Inoue *et al*, 2021	PCI	1998-2018	43	-	38/5	32/10	43/0	-	34/9	24-30/10-15	Baseline, before PCI	(12)
	Non-PCI		85	-	71/14	46/39	71/14	-	41/44			
Zhu *et al*, 2014	PCI	2003.1-2009.12	67	55.0 (34-82)	49/18	27/40	-	-	-	25/10	Baseline, before PCI	(13)
	Non-PCI		126	55.0 (7-74)	101/25	65/61	-	-	-			
Li *et al*, 2021	PCI	2013.7-2017.6	77	-	58/19	-	47/30	-	-	25/10	Baseline, before PCI,	(14)
	Non-PCI		113	-	74/39	-	43/70	-	-		MRI surveillance	
Mamesaya *et al*, 2018	PCI	2002.9-2015.8	60	64.0 (34-82)	43/17	8/52	58/2	-	23/37	25/10	Baseline, before PCI	(15)
	Non-PCI		20	72.5 (56-83)	11/9	6/14	11/9	-	4/16			
Ozawa *et al*, 2015	PCI	2006.1-2013.6	28	-	-	-	-	-	-	NR	Before PCI	(16)
	Non-PCI		57	-	-	-	-	-	-			
Pan *et al*, 2023	PCI	2006.1-2017.12	57	57.0	44/19	6/77	69/15	77/6	38/45	25/10	Baseline, before PCI	(17)
	Non-PCI		61	61.0	28/5	2/31	14/19	29/4	15/18			
Qi *et al*, 2022	PCI	2012.1-2018.1	75	-	53/22	23/52	35/40	-	16/59	-	Baseline, before PCI,	(18)
	Non-PCI		75	-	59/16	25/50	29/46	-	8/67		MRI surveillance	
Ghanta *et al*, 2021	PCI	2009-2020	243	65.2 (60-71)	91/152	58/185	221/13	-	69/174	25-36/10-18	Before PCI,	(19)
	Non-PCI		106	68.9 (61-74)	42/64	29/77	89/11	-	32/74		MRI surveillance	
Pezzi *et al*, 2020	PCI	1992-2012	205	62.2 (27-85)	110/95	-	-	67/14	70/23	25-30/10-15	Baseline, before PCI	(20)
	Non-PCI		92	68.6 (40-86)	52/40	-	-	34/8	36/28			
Farooqi *et al*, 2017	PCI	1985-2012	364	61.0 (34-85)	187/177	-	301/63	-	-	25/10	Baseline	(21)
	Non-PCI		294	64.0 (27-95)	155/139	-	230/64	-	-			
Sas-Korczyńska *et al*, 2017	PCI	2002-2015	167	59.0 (32-79)	103/64	-	100/67	-	-	30/15	Baseline	(22)
	Non-PCI		104	63.5 (35-79)	71/33	-	22/82	-	-			
Chen *et al*, 2018	PCI	2003.1-2015.12	19	(44-73)	15/4	10/9	-	-	-	25/10	Baseline	(23)
	Non-PCI		33	(38-74)	27/6	17/16	-	-	-			
Kim *et al*, 2019	PCI	1994.11-2010.6	139	60.0 (34-75)	123/16	34/105	-	-	-	-	Baseline	(24)
	Non-PCI		95	62.0 (40-77)	81/14	20/75	-	-	-			
Lee *et al*, 2023	PCI	2004.1-2017.12	211	65.0 (39-79)	175/36	41/170	191/20	-	32/158	25/10	Baseline	(25)
	Non-PCI		60	70.0 (44-93)	51/9	15/45	32/28	-	4/41			
Farris *et al*, 2019	PCI	2007-2018	39	62.0 (38-80)	20/19	12/27	-	-	12/27	25/10	Baseline	(26)
	Non-PCI		53	66.0 (41-91)	28/25	18/34	-	-	17/36			

Table I. Continued.

First author, year	Group	Time frame of the study	Patients, n	Median age (range), years	Male/female	I-II/III	CCRT/SCRT	EP/others	CR/PR	PCI dose, Gy/F	Brain MRI time points	(Refs.)
Yin *et al*, 2018	PCI	2010.1-2015.12	160	-		-	-	-	-	30-40/10-20	Baseline	(27)
	Non-PCI		109	-		-	-	-	-			
Held *et al*, 2022	PCI	2012.1-2019.12	28	62.2 (47-71)	12/16	-	-	28/0	-	25/10	Baseline	(28)
	Non-PCI		21	65.5 (57-71)	11/10	-	-	21/0	-			
Lim *et al*, 2022	PCI	-	26	60.0 (43-76)	22/4	-	-	25/1	-	25-37.5/10-25	Baseline	(29)
	Non-PCI		81	69.0 (44-82)	69/12	-	-	68/3	-			
Jeong *et al*, 2020	PCI	2005.8-2014.3	56	-		-	-	-	-	25/10	Baseline	(30)
	Non-PCI		45	-		-	-	-	-			

PCI, prophylactic cranial irradiation; CCRT, concurrent chemoradiothrapy; SCRT, sequential chemoradiotherapy; EP, etoposide and cisplatin; MRI, magnetic resonance imaging; CR, complete response; PR, partial response; F, fractions.

0.24-0.78; P=0.005; Fig. 5), indicating a significant decrease in BM rate in the PCI group. However, the combined results revealed that the PFS (HR, 0.62; CI, 0.38-1.02; P=0.059) and BMFS (HR, 0.47; CI, 0.19-1.17; P=0.105) in the PCI group were not significantly different from those in the non-PCI group (Fig. 5).

Results of the MRI surveillance group. The results of the 4 studies that used brain MRI for active surveillance following PCI revealed that the 1-, 2-, 3- and 5-year OS rates of patients in the PCI groups were 91, 74, 49 and 32%, respectively (Fig. S7), while in the non-PCI group the OS rates were 87, 61, 33 and 27% (Fig. S8). Notably, the combined HR was 0.65 (CI, 0.41-1.05; P=0.078; Fig. 6). Propensity-matched analysis was performed in 3 of the 4 studies that used brain MRI for active surveillance following PCI, and the pooled findings did not reveal a statistically significant difference in OS between the two groups (HR, 0.70; CI, 0.48-1.03; P=0.068; Fig. 3). The 1-, 2-, 3- and 5-year BM rates of patients in the PCI groups were 6, 26, 22 and 34%, respectively (Fig. S7), while in the non-PCI group the BM rates were 31, 57, 31 and 40% (Fig. S8). The combined HR was 0.6 (CI, 0.45-0.80; P=0.001; Fig. 6), indicating that the rate of BM in the PCI group was significantly decreased. The combined results also demonstrated that the PCI group exhibited significantly higher rates of PFS (HR, 0.76; CI, 0.64-0.90; P=0.001) and BMFS (HR, 0.24; CI, 0.13-0.43; P<0.001) than the non-PCI group (Fig. 6).

To investigate the heterogeneity of the OS analysis in the MRI surveillance group, a subgroup analysis was performed (Fig. 7). The variables used to analyze the heterogeneity of OS were the male/female ratio, median age (<70 vs. ≥70 years), proportion of stages (I-II/III) and fraction of CR/PR. The results of the subgroup analysis revealed that there was no significant difference in OS between the PCI and non-PCI groups in any of the subgroups.

Failure patterns. In total, 5 studies examined the failure patterns of LS-SCLC following treatment and demonstrated that the main cause of failure was extracranial failure. Notably, overall recurrence, extracranial progression alone, extracranial progression combined with intracranial progression, intracranial progression alone and overall intracranial progression rates in the PCI groups were 59, 51, 6, 6 and 21%, respectively (Fig. 8), while in the non-PCI groups the rates were 66, 43, 9, 14 and 33% (Fig. 9).

Bias and sensitivity analyses. The results of the funnel plot analysis revealed that there was no indication of significant publication bias (Fig. 10). Sensitivity analyses were performed to determine the effect of each study on the overall meta-analysis estimate, through calculating the pooled HRs and omitting one study at a time. The pooled results did not significantly differ when single studies were removed, suggesting that the results of the meta-analysis were stable (Fig. 11).

Discussion

The results of a previous meta-analysis revealed that PCI significantly decreased the incidence of BM by 25.3% (33.3 vs. 58.6%; P<0.001) and increased the 3-year OS rate by

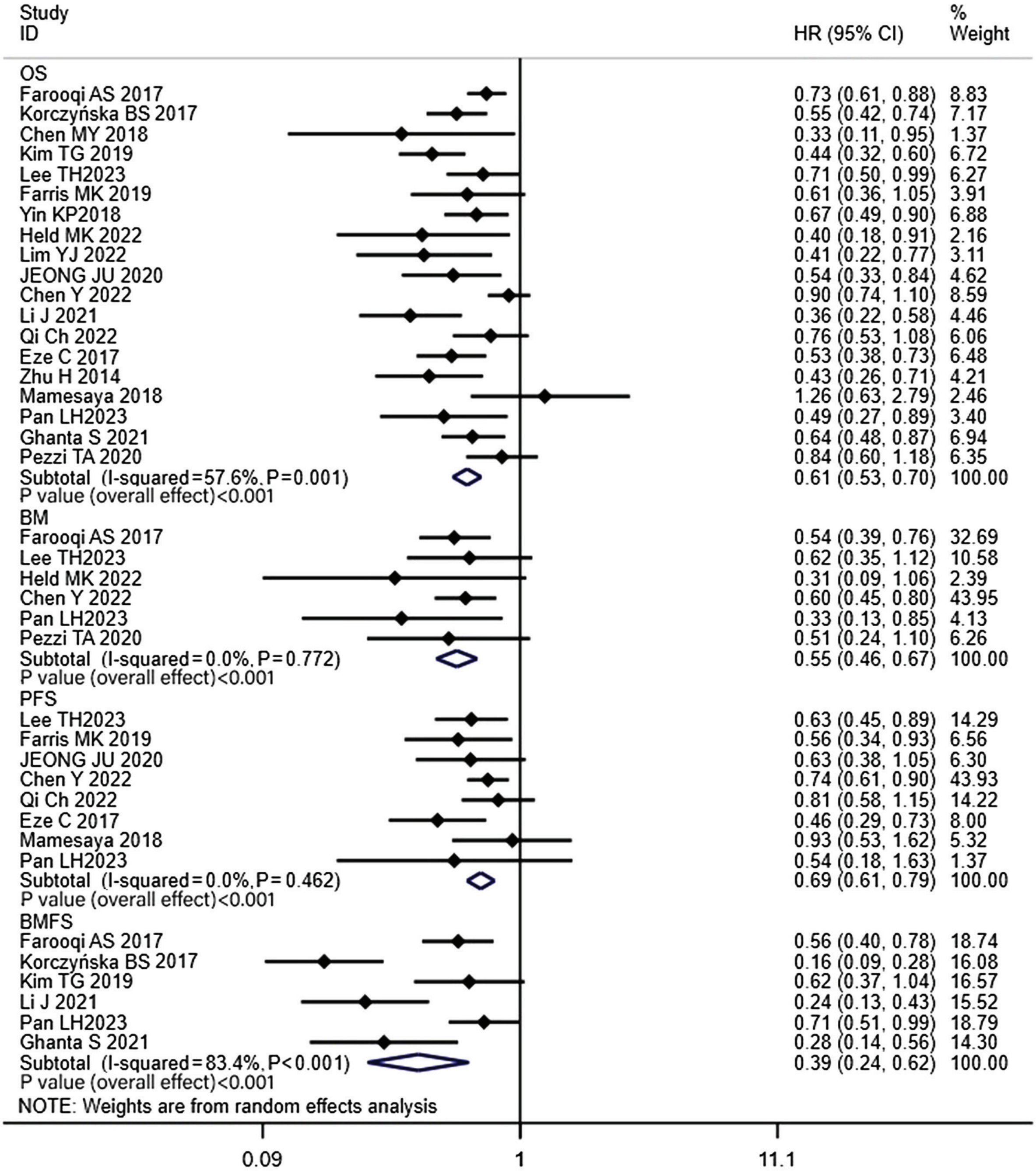

Figure 2. Forest plots for OS, PFS, BM and BMFS in all patients who did or did not receive prophylactic cranial irradiation. OS, overall survival; PFS, progression-free survival; BM, brain metastasis; BMFS, BM-free survival; HR, hazard ratio; CI, confidence interval.

5.4% (20.7 vs. 15.3%; P=0.01) in patients with LS-SCLC who achieved CR after chemoradiotherapy (6). PCI is the standard treatment recommendation for patients with LS-SCLC who achieve CR or PR with first-line chemoradiotherapy (7). The results of a previous study revealed a notable difference in the detection rates of BMs originating from SCLC between the CT and MRI eras (9). Notably, the observed rates of BM were 10 and 24%, respectively, indicating that MRI may be more effective for BM detection. However, the majority of the studies included in the previous meta-analysis utilized CT rather than MRI to assess the presence of BM in LS-SCLC. In a single-center study, 40 patients with LS-SCLC who achieved CR after chemoradiotherapy underwent cranial MRI prior to PCI (34). The results demonstrated that BM was detected in 13/40 patients (32.5%; 95% CI, 18-47%) and 11 cases exhibited asymptomatic BM. These results suggested that patients who did not undergo cranial MRI may have developed occult BM before or during treatment; thus, patients who underwent PCI in the pre-MRI era may have received treatment, rather than prevention. Thus, these results may have overstated the benefits of PCI. Based on the results of the aforementioned studies, numerous retrospective clinical studies have re-evaluated the effectiveness of PCI in patients with LS-SCLC during the MRI era (10-30). The results of the present meta-analysis indicated that PCI significantly decreased the incidence of BM (P<0.001) and prolonged the OS time (P<0.001) in patients with

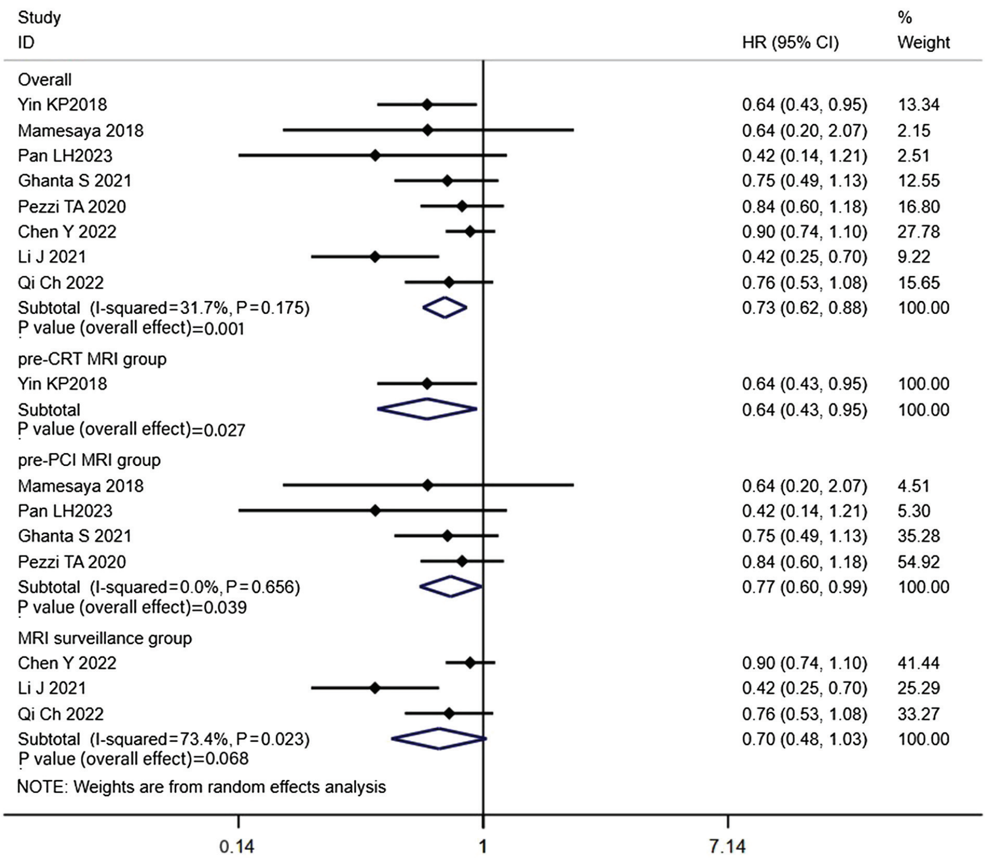

Figure 3. Forest plot of the OS of patients in the studies that used propensity matching analysis. OS, overall survival; HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; PCI, prophylactic cranial irradiation; MRI, magnetic resonance imaging.

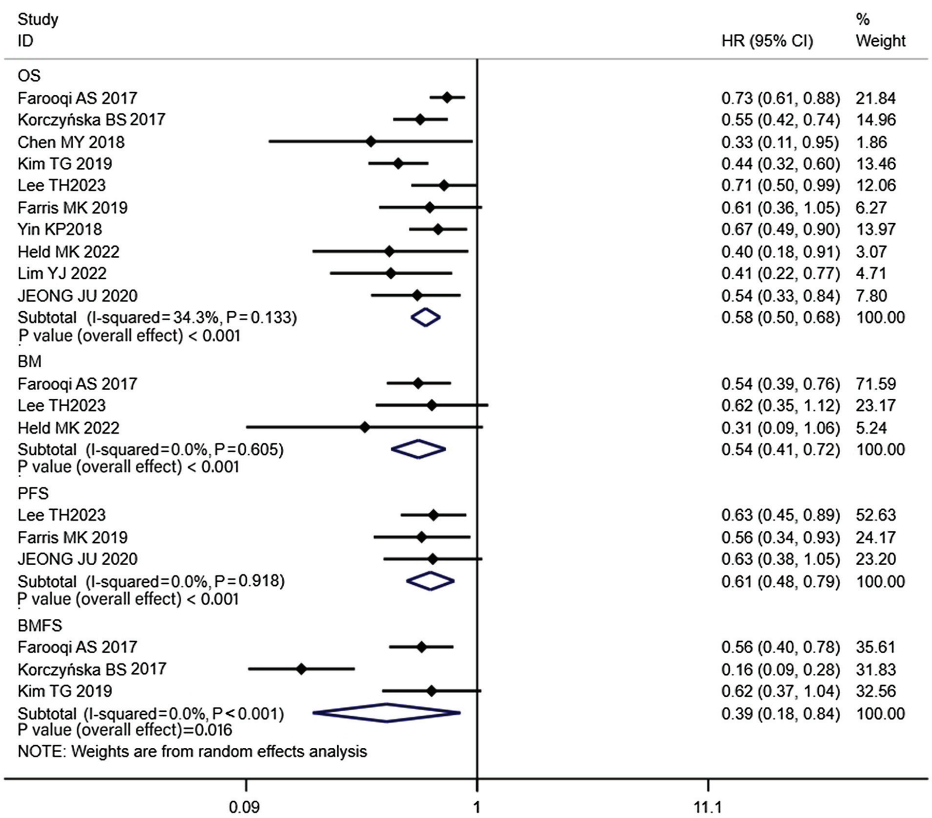

Figure 4. Forest plot for OS, PFS, BM and BMFS in the pre- chemoradiotherapy magnetic resonance imaging group of patients who did or did not receive prophylactic cranial irradiation. OS, overall survival; PFS, progression-free survival; BM, brain metastasis; BMFS, BM-free survival; HR, hazard ratio; CI, confidence interval.

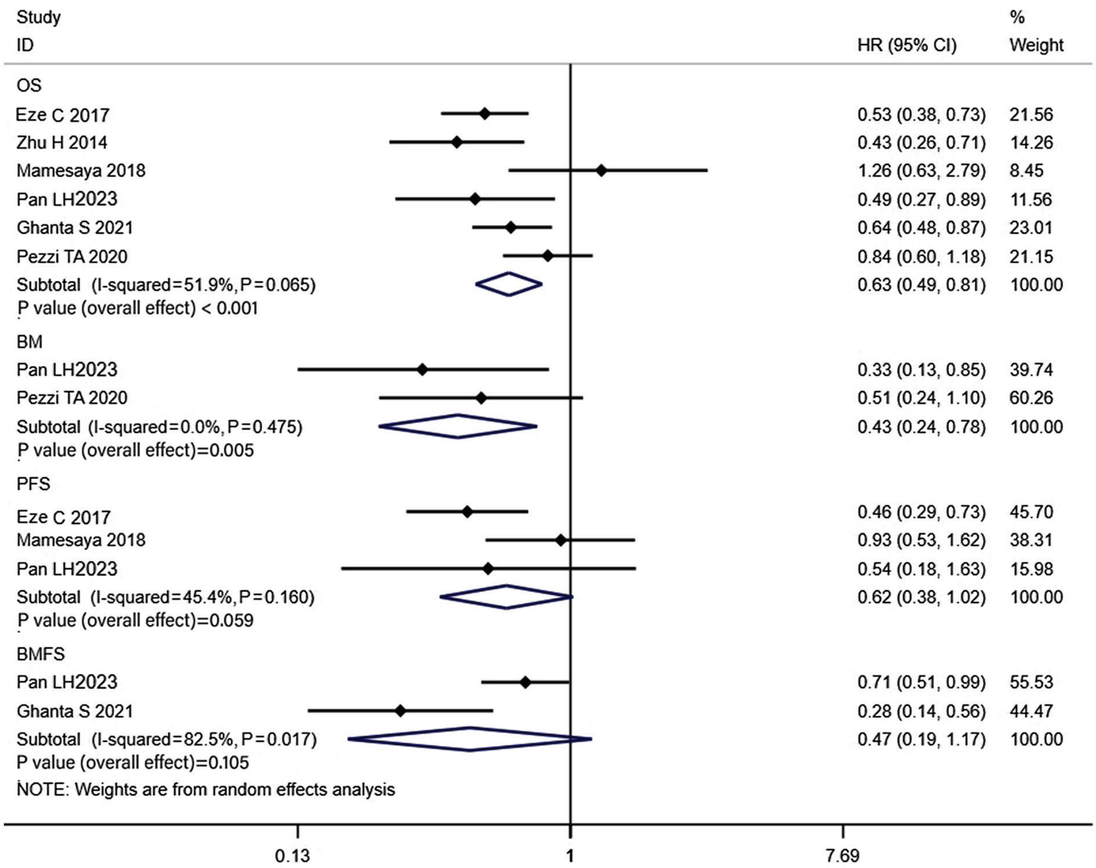

Figure 5. Forest plot for OS, PFS, BM and BMFS in the pre-PCI magnetic resonance imaging group of patients who did or did not receive PCI. OS, overall survival; PFS, progression-free survival; BM, brain metastasis; BMFS, BM-free survival; HR, hazard ratio; CI, confidence interval; PCI, prophylactic cranial irradiation.

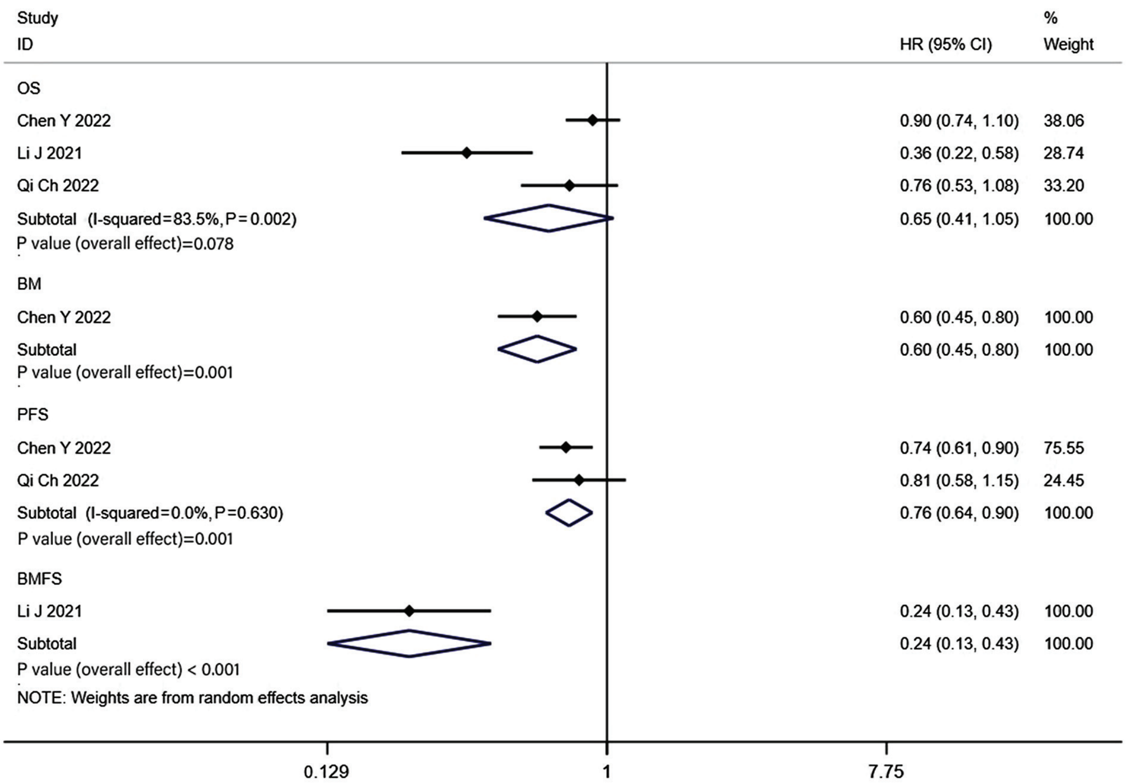

Figure 6. Forest plot for OS, PFS, BM and BMFS in the magnetic resonance imaging surveillance group of patients who did or did not receive prophylactic cranial irradiation. OS, overall survival; PFS, progression-free survival; BM, brain metastasis; BMFS, BM-free survival; HR, hazard ratio; CI, confidence interval.

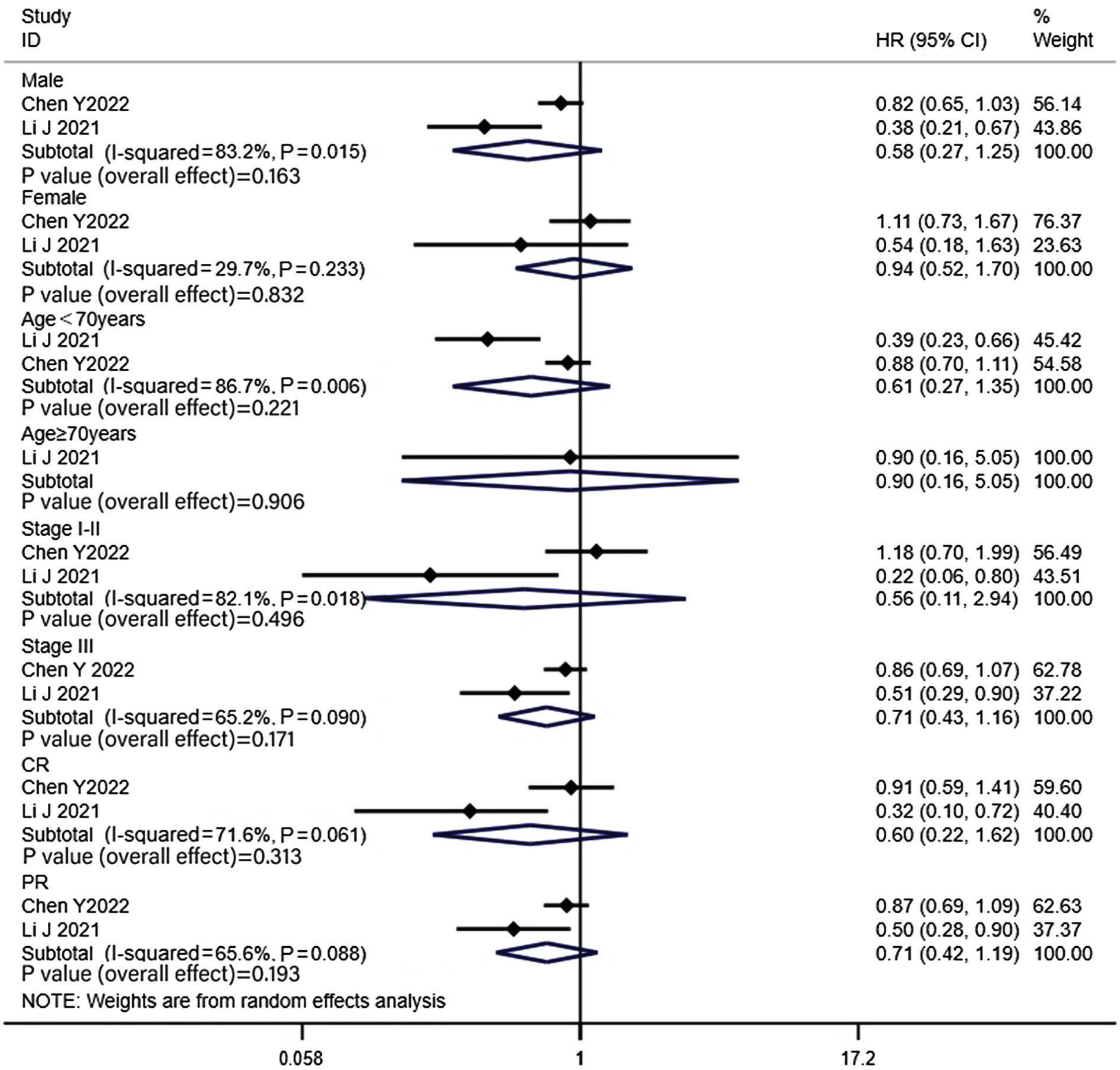

Figure 7. Forest plots for subgroup analysis of overall survival in the magnetic resonance imaging surveillance group of patients who did or did not receive prophylactic cranial irradiation. HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response.

LS-SCLC who had the absence of BM confirmed via brain MRI at baseline or prior to PCI. In addition, the results of the present meta-analysis revealed that studies using propensity score matching also revealed that PCI significantly prolonged OS time (P=0.039), which was consistent with the findings of previous meta-analyses (35,36). Thus, in the era of MRI, PCI is required for patients with LS-SCLC who have undergone brain MRI at baseline or prior to PCI, to exclude the presence of BM.

The results of a previous prospective study revealed that PCI did not significantly increase the OS time of patients with extensive-stage SCLC compared with active surveillance using brain MRI. Notably, the median OS time in the PCI and non-PCI groups was 11.6 and 13.7 months, respectively (HR, 1.27; 95% CI, 0.96-1.68; P=0.094) (37). Previous retrospective clinical studies have also investigated whether active surveillance using brain MRI is superior to PCI in patients with LS-SCLC (10,14,18,19). The results of the present meta-analysis revealed that PCI was able to significantly reduce the incidence of BM in patients with LS-SCLC compared with active surveillance using brain MRIs (P=0.001); however, the observed benefit in OS was not significant (P=0.078). The studies included in the present meta-analysis were retrospective clinical studies. Thus, there may have been differences in the baseline characteristics of the included patients. In addition, propensity score matching analysis was carried out in 3 of the studies to reduce the impact of potential confounding, through reaching an equilibrium between the baseline characteristics of the two patient groups. The combined results of the studies that used propensity score matching also demonstrated that PCI did not significantly prolong OS in patients with LS-SCLC, compared with active surveillance using brain MRIs (P=0.068). Notably, brain MRI follow-up may be for the early detection of BM, leading to timely treatment with salvage radiation therapy and improved patient survival. The results of the present meta-analysis also revealed that the 1-, 2-, 3- and 5-year BM rates were higher in the MRI surveillance group than in the pre-CRT and pre-PCI groups, indicating that active surveillance using brain MRI may be used for the early detection of asymptomatic BM. Moreover, studies included in the present meta-analysis demonstrated that salvage cerebrospinal radiotherapy was administered to 69.4-91.5% of patients in the

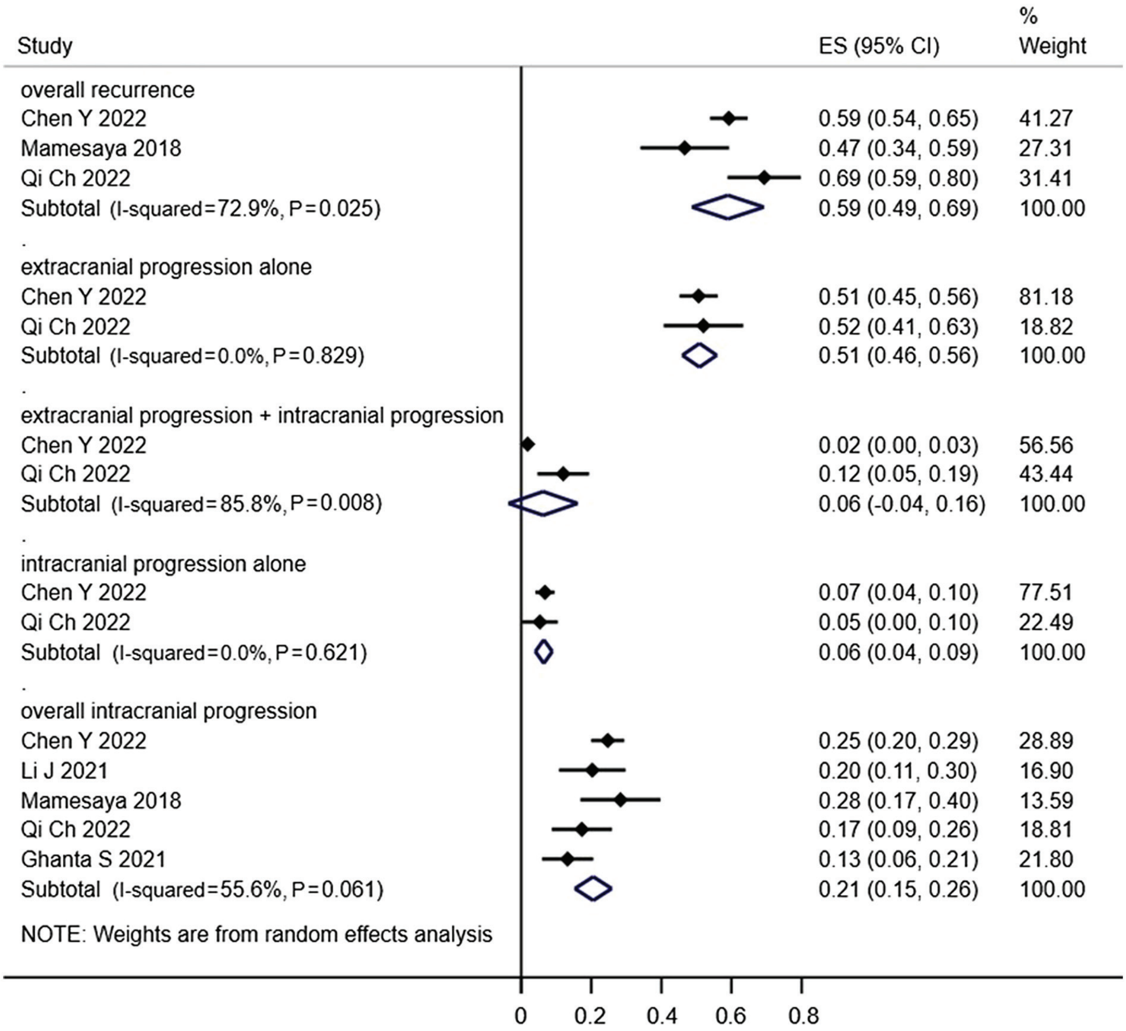

Figure 8. Forest plot of failure patterns in the prophylactic cranial irradiation group. ES, effect size; CI, confidence interval.

MRI surveillance group, compared with 23.1-58.5% of patients in the PCI cohort. These results indicated that the percentage of patients in the PCI group who received salvage radiotherapy following BM was lower; however, the effectiveness of systemic therapy for BM was suboptimal. This may have contributed to the poor prognosis of these patients. In addition, the results of previous studies demonstrated that patients with PR and stage III disease were at a higher risk of developing BM and may have been more likely to benefit from PCI (14,19). However, the results of the subgroup analysis in the present study revealed that PCI did not significantly improve the OS of patients with PR and stage III LS-SCLC, compared with active surveillance using brain MRI. Thus, even in patients at high risk of BM, brain MRI active surveillance and early effective salvage therapy may be not inferior to PCI in patients with LS-SCLC. Ongoing large-scale randomized clinical trials are focused on the effects of active surveillance using brain MRI and early effective salvage therapy in patients with LS-SCLC [NCT04790253 (38), PRIMALung (39) and SWOG1827 (40)].

The results of the present meta-analysis revealed that extracranial metastasis was the primary mode of recurrence following initial treatment for LS-SCLC. In addition, the results of a previous study revealed that intrathoracic recurrence alone was the most common mode of recurrence following treatment for LS-SCLC (28%), which was markedly higher than the incidence of BM (9%) (41). Although PCI may decrease the incidence of BM, the risk of extracranial metastasis remains high, which may impact the therapeutic efficacy of PCI. Thus, improved extracranial disease control may improve the observed benefits of PCI in patients with LS-SCLC. Following the introduction of immunotherapy, the ADRIATIC study (42) assessed the effectiveness of immunoconsolidation following immunotherapy combined with chemoradiotherapy for the treatment of LS-SCLC. The results demonstrated that treatment was well-tolerated and that the PFS (16.6 vs. 9.2 months; HR, 0.76; CI, 0.61-0.95; P=0.0161) and OS (55.9 vs. 33.4 months; HR, 0.73; CI, 0.57-0.93; P=0.0104) times of patients were improved. A trial including 40 patients with LS-SCLC demonstrated that immunotherapy combined with chemoradiotherapy was advantageous for patients with LS-SCLC, with median OS and median PFS times of 39.5 (CI, 8.0-71.0) and 19.7 (CI, 8.8-30.5) months, respectively (43). Notably, immunotherapy significantly increased the rate of systemic disease control in patients with LS-SCLC, which may have enhanced the therapeutic benefits of PCI. Therefore, in the era of immunotherapy, reassessing the curative value of PCI for patients with LS-SCLC is crucial.

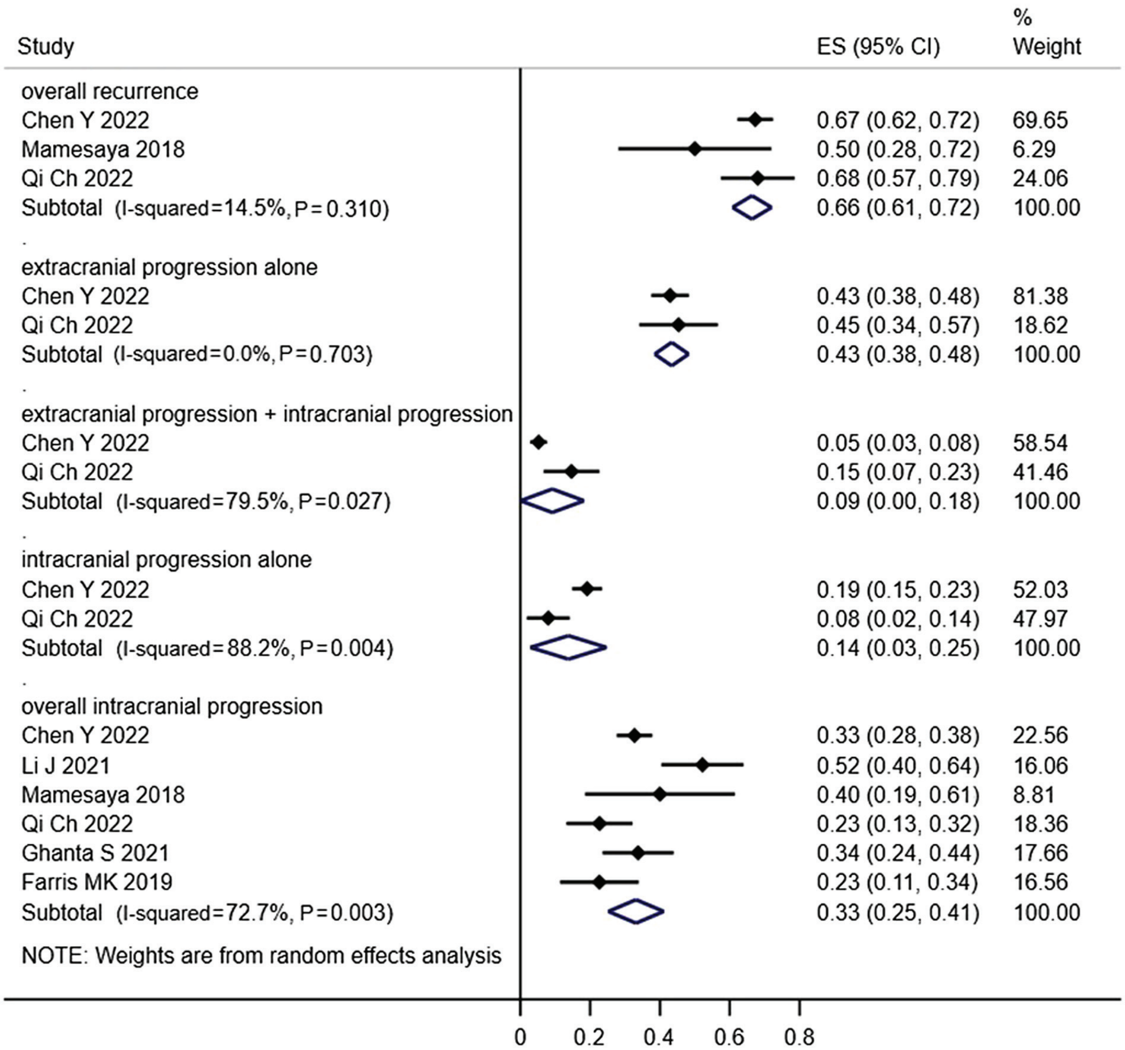

Figure 9. Forest plot of failure patterns in the non-prophylactic cranial irradiation group. ES, effect size; CI, confidence interval.

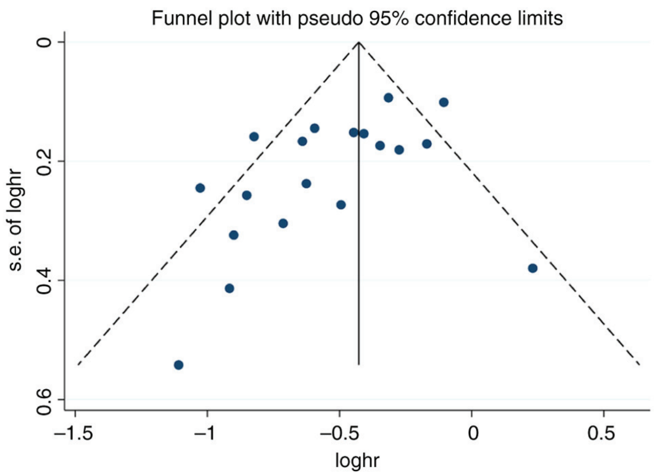

Figure 10. Funnel plot for overall survival. hr, hazard ratio; s.e., standard error.

Notably, the present study exhibits several limitations. The included studies were retrospective clinical studies, which may lead to selection bias and selective reporting. However, prospective studies focusing on the effects of PCI on LS-SCLC in the MRI era are ongoing and the results are yet to be reported. In addition, the included studies did not record or analyze neurotoxicity or cognitive function following PCI. Thus, post-PCI neurotoxicity response was not investigated in the present study. Moreover, the present study did not determine the impact of salvage therapy following BM on patient survival, as only a small number of the included studies described the use of salvage therapy following BM. In some cases, HR values were estimated based on Kaplan-Meier survival curves, as numerous included studies did not provide HR values. These factors may have limited the results of the present meta-analysis.

In conclusion, the results of the present meta-analysis revealed that PCI was effective in improving OS and reducing BM in patients with LS-SCLC, when the absence of BM had been confirmed using brain MRI at baseline or prior to PCI. In patients with LS-SCLC who underwent active surveillance using brain MRI following PCI, PCI reduced the rate of BM. However, PCI did not significantly improve OS. Notably, studies included in the present meta-analysis were retrospective; thus, additional randomized controlled clinical trials are required to verify the results.

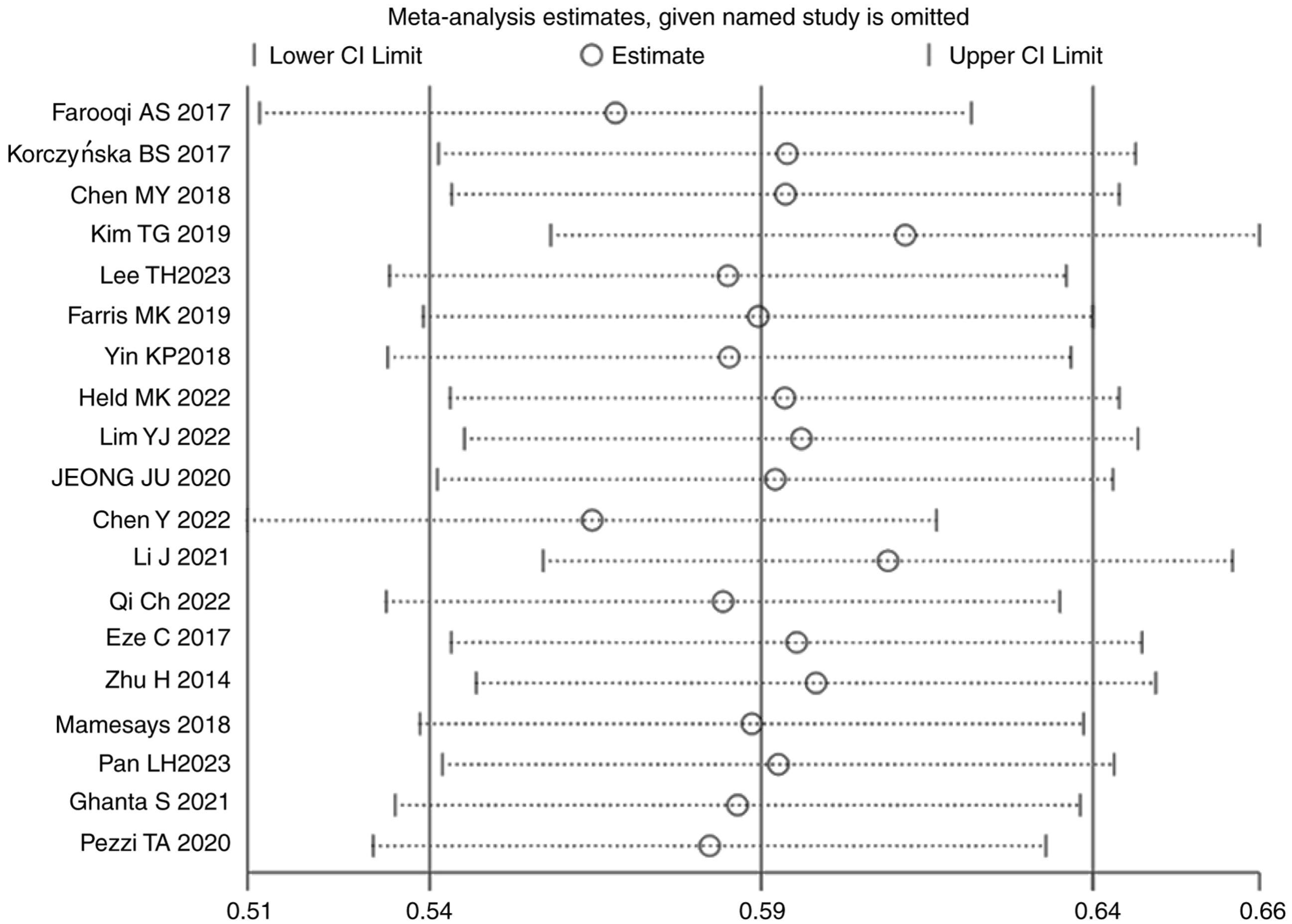

Figure 11. Sensitivity analysis of PCI vs. non-PCI for overall survival in limited-stage small-cell lung cancer. CI, confidence interval; PCI, prophylactic cranial irradiation.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LS was involved in the conceptualization and design the work and wrote the manuscript. YD, MJ, HS, LG and YQ were responsible for acquiring, analyzing and interpreting the data. HS and LG confirm the authenticity of all the raw data. JT and SW interpreted the data and designed the study, and all of the authors carefully reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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